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## Different Types of Childhood Adverse Experiences and Mood Disorders

Alessandra Alciati  
*Department of Psychiatry,  
 Luigi Sacco University Hospital, Milan  
 Italy*

### 1. Introduction

A growing body of studies has suggested that adverse events or conditions, particularly when experienced early in life, are associated with an increased risk to develop mood disorders (Agid et al., 1999). The most salient forms of childhood adverse experiences are parental loss, as well as sexual, physical and emotional abuse.

The first studies were focused on a single event, such as parental death or sexual abuse, theorizing a unique effect of a particular adverse experience on a single type of mental disorders, most often depression (Tennant et al., 1980).

Recent studies have shown that multiple categories of retrospectively reported childhood adverse events often co-occur (Finkelhor et al., 2007) and, in many cases, they are non-specific in their associations with different mental disorders (Green et al., 2010). On this basis, the latest studies (Green et al., 2010) are aimed to assess various forms of abuse simultaneously and to examine multiple psychiatric outcomes in order to avoid overly narrow interpretations.

Although the demarcation lines between these various forms of childhood adverse experiences are not easily drawn, it is important to maintain the distinctions in order not to obscure a possible specific effect of any particular type of adverse event.

This approach has been supported by a recent study showing that, among 25 negative factors considered, late-life depression was significantly associated with only 8: verbal abuse from parents, mental cruelty, excessive punishment by parents, abuse by an adult outside the family, parental mental disorder, poverty, home conflict and excessive sharing of parental problems with children (Ritchie et al., 2009). In agreement with this result, Danese et al. (2009) have shown that different childhood adverse experiences do not necessarily overlap and exert independent effects on adult major depression risk.

This chapter summarizes the findings of researches from selected publications focused on single childhood adverse events and the risk to develop depression in adulthood. Then, it considers the neurobiological changes related to childhood adverse experiences and their relationship with the development of depression in adulthood.

## 2. Childhood adverse experiences and mood disorders

### 2.1 Childhood parental loss

An extensive literature, dating back to the work of Freud (1917), focused on childhood separation from parents due to death, illness, divorce or otherwise, as an antecedent to adult depression.

The death of a parent, which is experienced by 4% of children and adolescents in Western countries, is rated as one of the most stressful life events that a child can experience (Harrison & Harrington, 2001). Earlier reviews of the literature on this topic have not been consistent with each other: Crook & Eliot (1980) and Tennant et al. (1980) concluded that parental death in childhood has little effect on later development of depression, whereas Lloyd (1980) found that the childhood death of a parent increases the depressive risk by a factor of about 2 or 3. Reviews conducted in the late 80s concluded that, although there is no evidence that parental death is a significant risk factor for depression, separations, particularly those occurring in the context of family discord, seem to contribute to adult depression (Brown et al., 1986; Tennant, 1988). Studies based on patients who were hospitalized for severe depression and/or attempted suicide have found a higher prevalence of parental death among severe depressed subjects than in the general population (Kunugi et al., 1995; Munro, 1966).

Many studies have investigated the relationship between childhood parental loss and bipolar disorder, but their results are far from conclusive. Perris found that parental death in childhood was not more frequent in bipolar and unipolar patients than in the general population (Perris et al., 1986); furthermore, Furukawa et al. (1999) compared the rates of parental death and separation among bipolar patients and normal controls and found no statistically significant differences between the groups. On the contrary, other studies have shown that the loss of a parent during childhood significantly increases the likelihood of developing a bipolar disorder during adult life (Agid et al., 1999; Mortensen et al., 2003).

These inconsistencies are largely attributed to substantial methodological limitations, such as a sample consisting only of females or subjects who sought psychiatric services and, in older studies, the lack of symptom-based and standardized diagnostic criteria. Moreover, the failure to control for variables that could affect pathology (gender and current age of the participant, gender of the deceased, life events, socio-economic status) might have contributed to some inconsistencies of the findings.

Additional methodological problems, such as the differential death rates between men and women who are in the parenting age, make difficult to examine the effects of death by the sex of the deceased. Epidemiological data on parental death in childhood indicate that fathers die twice as frequently as mothers and, in addition, surviving fathers tend to be less willing to participate in research and to seek help when distressed (Gersten et al., 1991). Van Eederwegh et al. (1982) have found a link between the death of a father and severe depression in boys and older children, and Kendler & Baker (2007) reported that childhood parental loss was a more potent predictor of adult depressive episodes in males, compared to females. More recently, Jacobs & Bovasso (2009) have shown that, while maternal death was not a predictor of adult pathology, paternal death more than doubled the increased risk of major depression in adulthood. These results suggest that the father's death is a severe loss as the death of the mother. Financial complications may contribute to the effect of the

father's death in childhood on adult depression, especially in a sample where the participants' childhood took place before 1960, when the discrepancies between men and women's income were greater than today (Jacobs & Bovasso, 2009).

It is conceivable that parental death could have a differential impact according to the age of the child because the level of emotional and cognitive development will influence the understanding of events and the response to the parental death. While some investigators have reported that the risk of developing a mood disorder following childhood parental loss is greater when the loss occurs during early childhood (Agid et al., 1999), others have not found such association (Kendler et al., 1990; Jacobs & Bovasso, 2009). Girls under the age of 11 years who lost their mother by separation or by death were reported to be at higher risk of depression in adult life (Brown et al., 1977), but the parental death increasing the risk for depression also applied to female subjects who lost parents between the age of 11 and 17 years (Barnes & Prosen, 1985). Bifulco et al. (1987) found that maternal loss doubled the risk for depression and anxiety in women and the effect was greater in those women who lost their mothers before the age of 6 years. In a meta-analysis of the literature, Patten (1991) found a significant association between maternal loss before the age of 11 years and depression in females.

Modes of parental death are associated with offspring long-term psychiatric morbidity severity. Recent evidence has shown that unnatural death of a parent during childhood and adolescence has a stronger association with psychiatric sequelae than sudden natural parental death (Wilcox et al., 2010). War-related loss of the father during childhood or adolescence strongly contributes to distress and disability in adulthood: 22% of bereaved children and adolescents and 11% of non-bereaved war survivors met the criteria for a major depressive episode a decade after the war (Morina, 2011). Children, whose parents died by suicide, are at greater risk for adverse outcomes, compared with offspring whose parents died from other causes (Brent, 2009). The association between bipolar disorders and parental suicide, suggested in earlier studies, has been supported by two investigations. Mortensen et al. (2003) found an increased risk for bipolar disorders among the children of parents who committed suicide, and Kessing et al. (2004) observed that an experience of maternal suicide has been associated with a history of mania or mixed episode upon first admission to psychiatric hospitals. No effect of maternal death due to a non-suicidal cause was found.

Few early studies have clearly differentiated between the psychological consequences of parental death and separation, referring to parental loss without making any distinction between the two experiences. However, the psychiatric outcome of the two types of childhood parental loss can be expected to be very different. Harris et al. (1986) made the distinction between loss by death or by separation in their sample and concluded that the rate of depression was almost the same among women with a loss of their mother by death (23%) and separation (21%). A scarce effect of childhood parental loss on adult depression has been found in a community sample, with no significant differences between the effect of death and separation (Tennant et al., 1982). Data from a community survey have shown that women, who were diagnosed with major depression, reported parental divorce or separation before the age of 17 years significantly more often (33%) than controls (14%), but without any significant effect of parental death (Harris et al., 1986). Similarly, several studies have suggested that childhood parental separation involves a greater risk of development of

adult depression than the death of a parent. In a community sample, the association between prolonged separation from both parents and the increased risk of depression in women was stronger than for death or separation from one parent (Oakley Browne et al., 1995). Agid et al. (1999), in a case-control study, have found that the loss of a parent before the age of 17 years was significantly associated with major depression in adulthood; however, when the type of loss was categorized, the difference was significant only for permanent separation from a parent. In a study on high school students, adolescents who had experienced separation from parents had more anxious and depressive symptoms than those belonging to intact families, while the death of a parent was not associated with significantly different symptom scores. Separation from both parents was significantly more detrimental to the adolescent than separation from only one parent, probably because it reflects serious difficulties in parenthood (Canetti et al., 2000). The absence of one parent after divorce is very common and it does not always lead to psychological problems, unlike parental disharmony (Tennant et al., 1988).

These findings suggest that separation may be understood by the child as an event with more negative connotations than parental death. While separation may be perceived by the child as voluntarily made, even at the cost of distance from the child, death is an event that the parent could not avoid. Moreover, studies have highlighted a process of idealization of the parent after death, while such process has not been observed after separation from a parent. Adult psychiatric patients and normal controls perceive their parents already died in a more positive manner than the subjects whose parents are still alive (Richter et al., 1992).

## 2.2 Physical and sexual abuse

A Canadian province-wide survey of approximately ten thousand people showed that 27% of females reported having suffered either physical or sexual abuse or both during childhood (MacMillan et al., 1997). In a community sample of more than eight thousand subjects, a significant association between a history of physical or sexual abuse in childhood and major depression (followed or not by a manic episode) and a strong relationship between childhood physical abuse and mania have been found (Levitan et al., 1998). One study including almost 2000 women, who were seen in primary care practices, revealed that the subjects who reported childhood physical and/or sexual abuse had higher scores of depression and anxiety and had attempted suicide more frequently than women without a history of childhood abuse (McCauley et al., 1997). Hyun et al. (2000) found that a history of childhood physical and sexual abuse was significantly more frequent in bipolar than in unipolar adults. Wise et al. (2001) have shown, in a case-control study, that women who suffered physical abuse during childhood are three times more likely to experience adult depression than others. Women who were abused in childhood are four times more likely to develop syndromal major depression in adulthood than women who were not abused, with the magnitude of the abuse correlated with the severity of depression (Mullen et al., 1996). This result has been later replicated by a study showing that female subjects, who reported experiences of childhood physical or sexual abuse, had a three-to-four-fold increase in the lifetime prevalence of major depression (MacMillan et al., 2001).

Several studies have reported an association between mood disorders and childhood sexual abuse alone. Prevalence rates of sexual abuse in children range from 3.0% to 33.2% (Dube et al., 2005), but these values are likely to be underestimates because of the frequent



underreporting of sexual abuse (Priebe & Svedin, 2008). Moreover, a significant variability in the percentage of documented survivors who recall the abuse as adults has been found (62%-81%) (Goodman et al., 2003). Molnar et al. (2001) examined the associations between childhood sexual abuse and a range of mood, anxiety and substance-related disorders in a nationally representative sample of nearly 6000 individuals in the United States. The percentage of women with lifetime depression was 39.3% among those reporting childhood sexual abuse, compared with 21.3% in the general population, as the rate reported by the National Comorbidity Survey (Kendler et al., 2000). Chronic childhood sexual abuse perpetrated by a close relative or other trusted acquaintance has more severe long-term consequences than isolated incidents committed by strangers. Among women treated for anxiety disorders and/or depression, the subjects with a history of childhood sexual abuse have a significantly higher load of all types of childhood adversities, compared to patients without any abuse, due to a greater number of family background risk factors. The lack of parental protection and an environment described as non-supportive, with conflict, violence and marital turbulence, were the most commonly family background risk factors associated with childhood sexual abuse (Gladstone et al., 1999).

Because most studies have used cross-sectional designs and relied to a large degree on retrospective self-report data, a method that risks having a range of retrospective biases, longitudinal studies are needed to provide information about the causal relationship between childhood sexual and/or physical abuse and mood disorders and to systematically evaluate developmental trajectories. The first prospective assessment of the risk of depression in a group of children with documented physical, sexual abuse and neglect and a matched comparison group, followed up in adulthood, has shown that childhood physical abuse was associated with an increased risk for lifetime major depression, in agreement with earlier cross-sectional studies (Widom et al., 2007). The same study has not found any relationship between childhood sexual abuse and lifetime or current major depression, but abused subjects reported more depressive symptoms than controls. Differences in the design of the studies (prospective longitudinal with documented cases of maltreatment versus cross-sectional and based on retrospective recall) may in part account for the discrepancy between these results and the larger extant literature. A systematic review of longitudinal studies of childhood maltreatment and psychiatric outcomes (between 2000 and 2008) found an association between childhood maltreatment and depression, PTSD, and suicide attempts (Gilbert, 2009). A recent review and meta-analysis of 37 longitudinal observational comparative studies found an association between a history of sexual abuse and a lifetime diagnosis of anxiety, depression, eating disorders, PTSD, sleep disorders, and suicide attempts that persisted regardless of the survivor's sex or age at which abuse occurred. Associations between sexual abuse and depression, eating disorders and post-traumatic stress disorder were strengthened by a history of rape (Chen et al., 2010).

There is growing evidence that childhood sexual and physical abuse leads to dysregulation of the hypothalamic pituitary-adrenal (HPA) axis in children (Cicchetti & Rogosch, 2001) that has enduring effects on cortisol responses to stress in adulthood (Heim et al., 2000). Women with severe physical or sexual abuse and neglect were more likely to exhibit endogenous depressive subtypes which have been associated with HPA axis dysregulation (Harkness & Monroe, 2002). Women with current depression and a history of childhood physical and/or sexual abuse had greater increases in plasma cortisol and ACTH in response to a laboratory psychological stress test (Heim et al., 2000). The role of childhood

abuse has been further supported by the studies showing that patients with major depressive disorder and without a history of childhood abuse had a normal cortisol response to a psychological stress paradigm (Heim et al., 2000). Increased levels of cortisol during repeated childhood abuse, along with persistent sensitization of the HPA axis in adulthood, have been demonstrated to damage hippocampal neurons in adult women with major depressive disorder. Magnetic resonance imaging (MRI) has revealed reductions in hippocampus and amygdala (Schmahl, 2003) volumes as well as deficits in verbal declarative memory, measured with neuropsychological testing, in women who were sexually abused as children (Teicher et al., 2000). Evidence of the effects of traumatic stress in childhood on the hippocampus provides a possible neurophysiologic explanation for a phenomenon identified in studies of adults whose childhood abuse was documented, showing that their retrospective reports of childhood abuse underestimate the actual occurrence (Priebe & Svedin, 2008).

### 2.3 Emotional abuse

Emotional abuse encompasses several forms of childhood maltreatment, such as the witnessing of domestic violence and exposure to verbal aggression (Bernstein, 1997). It is not always recognized as a distinct form of maltreatment: some researchers have suggested that emotional abuse is inherent in all forms of maltreatment (Garbarino, 1986), while other investigators have demonstrated that it occurs independently of other types of abuse (Claussen & Crittenden, 1991). This second hypothesis has been supported by a study demonstrating that emotional abuse and neglect predicted adult psychopathology even after controlling the effects of other types of adverse experiences, such as physical and sexual abuse (Spertus et al., 2003).

Emotional abuse has been considered by some theorists as a non-specific risk factor for psychopathology in adulthood, while others have hypothesized that it may contribute to specific vulnerability to the development of depression. For example, Rose & Abramson (1992) hypothesized that childhood emotional abuse should be more likely to contribute to the development of a cognitive vulnerability to depression than physical or sexual abuse, because the depressive cognitive style is directly provided to the child by the abuser. In support of this theory, Gibb et al. (2003) reported that adult psychiatric outpatients with a history of childhood emotional abuse had a much higher rate of current depressive disorders than anxiety disorders. In contrast, reports of childhood physical and sexual abuse were equally strongly related to both depressive and anxiety disorders.

Several other studies support the relationship between emotional abuse and increased levels of depression (Briere & Runtz, 1988; Mullen et al., 1996; Rich et al., 1997) and suicidality (Briere & Runtz, 1988) in adulthood. Briere & Runtz (1988) demonstrated shared effects of multiple types of abuse in a sample of university women. However, even when these shared effects were statistically accounted for, paternal psychological abuse remained a significant predictor of anxiety, depression, interpersonal sensitivity, and dissociation in these women.

The impact of emotional abuse varied with the gender of abusers: children emotionally abused by their female caregivers were more prone to develop adult depressive symptoms, whereas subjects abused from a male family member had a negative impact on adult sexuality (Mullen et al., 1996).

Teicher (2006) has demonstrated that the exposure to verbal abuse alone and to witnessing of domestic violence alone had moderately strong effects on depressive symptoms. The combined exposure to verbal abuse and witnessing of domestic violence had a greater additive negative effect, having the exposed subjects depression scores that were 2.8 times as high as those of the non-abused subjects. The effect of the combined exposure to verbal abuse and witnessing of domestic violence was greater than or equal to the effect of exposure to familial sexual abuse.

According to the attachment theory (Bowlby, 1982), it is hypothesized that the cognitive models developed on the basis of the negative pattern of interactions between the emotionally maltreating parent and the child provide a set of negative beliefs and expectations about the self and the others, centred on shame, vulnerability to harm and self-sacrifice, which contribute to the development of later psychiatric symptoms.

Although attempts have been made to define childhood verbal abuse, there is not yet an operational definition of it nor is there a consensus about the prevalence of childhood verbal abuse in the general population. Even though the exposure to verbal aggression has received little attention as a specific form of abuse, it may be common as 63% of American parents reported one or more instances of verbal aggression against their child (Vissing et al., 1991). Children who reported frequent verbal aggression exhibited higher rates of interpersonal problems than other children. A relationship between maternal verbal abuse during childhood and a higher risk of developing several personality disorders (borderline, narcissistic, obsessive-compulsive, and paranoid) has been demonstrated and it has remained significant after controlling for temperamental features and co-occurring psychiatric disorders, physical and sexual abuse, neglect and parental psychopathology (Johnson, 2001).

## 2.4 Emotional neglect

The Centers for Disease Control and Prevention (CDC) define neglect as “failure to provide for a child’s basic physical, emotional, or educational needs or to protect a child from harm or potential harm” (Leeb et al., 2008).

Child neglect is the most prevalent, but least empirically studied, form of child maltreatment. Researches in this area are inherently difficult because neglected children may suffer both different subtypes of neglect and several associated adversities, such as physical or sexual abuse, witnessing of domestic violence, poverty, etc., that may confound the relationship between child neglect and adult development of depression or other psychiatric disturbances.

Emotional neglect has been defined as ‘emotional unresponsiveness, unavailability and neglect characterized by lack of interaction between parent and child’ (Glaser, 2002). It is generally characterized by parents who are emotionally and psychologically unavailable, detached, avoidant and unresponsive to their child’s needs and desires.

The attachment between the mother and her infant is one of the most important developmental interactions in mammals. The infant maintains closeness to his caretakers through an attachment system consisting of emotive and behavioural response patterns facilitating the capacity for self-perception and perception of others, a process also known as



mentalization (Bowlby, 1982). Frequent touching by the maternal caregiver is a biologic necessity for physical and psychological growth, as shown in infant rats and monkeys in which maternal deprivation results in persistent deficits of prefrontal executive function with impairment in social, behavioural and cognitive development (Black, 1998). Together with genetic predisposing factors, individuals with depressive manifestations in adulthood often show dysfunctional parental attachment. The study of Stansfeld et al. (2008) has demonstrated that, among the dysfunctional parental bonding, emotional neglect and mainly overprotection, characterized by parental intrusive behaviour, are strongly associated with depression. The same study has shown a correlation between attachment style and socio-demographic factors. Lower social class is robustly associated with emotional/material deprivation and low parental warmth. Less warm attachment relationships have been demonstrated to be a risk factor for the development of psychiatric symptoms in adulthood, particularly depressive symptoms. High parental warmth, which is more prevalent in upper socio-economic classes, is correlated with a decreased risk for insecure attachment styles.

The association between parental emotional neglect in childhood (assessed using the Parental Bonding Instrument (PBI) and the Childhood Experience of Care and Abuse (CECA) interview) and adult depression has been widely replicated (Parker et al., 1995; Hill et al., 2001; Bifulco et al., 2002). The result of a recent longitudinal study (Widom et al., 2007) has underlined the need to detect and to treat the long-term psychological sequelae of childhood neglect, showing that approximately one quarter of the neglected children in a sample of about 1200 subjects met the criteria for lifetime major depression and 15% for current depressive episode.

Despite this evidence, the developmental trajectories from emotional neglect to adulthood psychopathology are still poorly understood.

Childhood is a period of great vulnerability of the central nervous system to environmental factors. In the first years of life, children are most vulnerable to the effects of emotional neglect (Hildyard & Wolfe, 2002). From the postnatal period until the age of seven years, several processes (proliferation, migration, differentiation, synaptogenesis) affecting cognitive functions and emotional regulation take place (Keverne, 2004). Childhood adverse experiences are associated with abnormalities in brain development, particularly *Corpus Callosum* (CC) morphology, and neglect is the strongest experiential factor, accounting for a 15%–18% reduction in several *Corpus Callosum* regions (Teicher et al., 2004).

Neglected children may have difficulty in discriminating emotional expression (Fries & Pollak, 2004) and show various attention and social deficits (Turgeon & Nolin, 2004). The lack of emotional interaction during the crucial early period of development can result in poor emotional regulation that may be part of a cascade of adverse neurobiological events rendering a child vulnerable to the effects of later adverse experiences and triggering a vicious cycle towards adult depression.

### 3. Neurobiology of childhood adverse experiences and mood disorders

The exact neurobiological mechanisms through which childhood adverse experiences may increase the risk of developing depression are not yet known, but they may include

sensitization to later life events, mediated by some combination of neurobiological changes. The possible impact of such adversity on both brain structure and function involves the activity of the hypothalamic-pituitary-adrenal (HPA) axis, specific cerebral areas and genetic factors.

### **3.1 Hypothalamic-pituitary-adrenal (HPA) axis response to childhood adverse experiences**

It has been theorized that one neurobiological mechanism, which occurs as a consequence of childhood adverse events and results in effects that ultimately trigger depression after additional stress, is the increased activation of the hypothalamic-pituitary-adrenal (HPA) axis.

Several animal and human studies have shown that depression is associated with altered regulation of HPA axis activity, as indicated by elevated cortisol, disruption of circadian HPA rhythms, and failure to suppress cortisol levels following the administration of the synthetic steroid dexamethasone (Thase, 2002).

The hypothalamic-pituitary-adrenal (HPA) axis - which consists of the hypothalamus, the pituitary gland and the adrenal gland - is a critical component of the body's stress response system. Upon exposure to stress, neurons in the hypothalamic paraventricular nucleus (PVN) secrete corticotropin-releasing factor (CRF), which stimulates the production and release of adrenocorticotropin (ACTH) from the anterior pituitary region that, in turn, stimulates the release of glucocorticoids from the adrenal cortex. Glucocorticoids exert a negative feedback control on the HPA axis by the activity on mineralocorticoid and glucocorticoid receptors in the hippocampus, PVN, and the pituitary gland, in order to modulate responsiveness and to return the system to homeostasis (Jacobson & Sapolsky, 1991).

Laboratory animal studies have provided direct evidence that early stressful experiences influence the development of the hypothalamic-pituitary-adrenal (HPA) axis, leading to heightened stress reactivity that persists in adulthood. Early stress experimental paradigm, such as maternal separation in rats or adverse rearing conditions in non-human primates, produces long-lived hyperactivity of CRF neuronal systems as well as greater reactivity of the hypothalamic-pituitary-adrenal (HPA) axis to stress in adulthood (Ladd et al, 1996). Maternally separated adult rats also exhibit up to three-fold increases in ACTH and corticosterone responses to psychological stressors, when compared to control rats (Plotsky and Meaney, 1993).

Several clinical studies have documented the HPA axis involvement in man. Studies on the possible link between child maltreatment and HPA axis dysregulation in children have yielded inconsistent results. In a sample of prepubertal maltreated depressed, non-maltreated depressed and healthy control children, Kaufman et al. (1997) did not find any differences in cortisol measures, but the maltreated-depressed group exhibited elevated total, peak and net ACTH response in response to CRH, compared to the other groups of children. A study carried out on 175 maltreated children and 209 controls found no differences in morning or evening salivary cortisol measures between groups (Cicchetti and Rogosch, 2001). However, differences emerged when abuse subtype was considered. Children who had been both physically and sexually abused showed much higher morning

cortisol levels, compared to the emotional abuse, neglect, physical abuse alone and control groups, with a positive correlation between the severity of sexual abuse and cortisol levels.

Among studies that examined the relationship between child maltreatment and HPA axis function later in life, those which used psychosocial stressors to examine the HPA axis response and negative feedback inhibition are particularly interesting. Maltreated women with and without current MDD exhibited higher plasma ACTH levels in response to a standard psychosocial stress than women with no history of maltreatment and a current diagnosis of major depression and healthy controls with no history of maltreatment (Heim et al., 2000).

Sustained glucocorticoid exposure interferes with the normal transcriptional mechanisms that control the expression of Brain derived neurotrophic factor (BDNF), a protein that promotes the survival of selected neuronal population, with adverse effects on hippocampal neurons, particularly in the CA3 region, and prefrontal cortex (PFC). In these cerebral regions, reduction in dendritic branching, loss of dendritic spines, impairment of neurogenesis, increased rate of neuronal death and atrophy have been observed. Such damage might progressively reduce the ability of hippocampus and prefrontal cortex to exert the inhibitory control over the HPA axis activity, resulting in greater exposure to glucocorticoids (Nestler et al., 2002), a condition that has shown to play a role in the development of adult depression.

Hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis in major depression is suggested by a large body of research, including basal and provoked measurements of plasma HPA axis hormone concentrations, imaging of pituitary and adrenal gland volume, cerebrospinal fluid (CSF) levels of corticotrophin-releasing hormone (CRH), and *post-mortem* measures of brain CRH receptor binding and CRH messenger ribonucleic acid (mRNA) levels (Heim et al., 2008).

### **3.2 Structural brain changes associated with childhood adverse experiences**

Preclinical studies have shown an association between the prolonged exposure to glucocorticoids and the atrophy of brain regions involved in the regulation of HPA activity, such as the hippocampus (Sapolsky, 2000) and the medial prefrontal cortex (mPFC), in particular the anterior cingulate cortex (ACC) (Cerqueira et al., 2005).

A large body of research has investigated the relationship between childhood adverse events and changes in brain structures both in children who have experienced maltreatment and in adults reporting childhood adversity. The brain imaging studies included in this section are cross-sectional, therefore no conclusions can be drawn about the causal effect of maltreatment on the brain structures. We cannot exclude that the reported brain differences might represent a risk factor for exposure to maltreatment that, in turn, increases the risk of developing psychiatric symptoms or disorders.

#### **3.2.1 Hippocampus**

Several studies have been focused on the hippocampus, given its well-established role in regulating HPA activity, and the high density of glucocorticoid receptors expressed. The hippocampus plays a central role in declarative memory functions that are important in

accurately identifying the signal of potential threat during stress situations and it is involved in fear responses.

MRI studies of children and adolescents with PTSD following maltreatment (Jackowski et al., 2009) have consistently failed to detect the pattern of reduced hippocampal volume that has been generally reported in adults who have experienced maltreatment as children (Vythilingam et al., 2002). One possible explanation to account for the discrepancy of findings from children and adults comes from the so-called “neurotoxicity hypothesis”, which considers that years or decades of stress induced prolonged exposure to glucocorticoids could lead to a loss of hippocampal cells.

### 3.2.2 Amygdala

The amygdala plays a central role in differentiating threatening from non-threatening environmental stimuli on the basis of prototype matching to fear memories. The stimulation of amygdala in primate studies activates fear centers in the brain and results in behaviours consistent with anxiety, hyperarousal and hypervigilance. Results from human studies suggest that the amygdala is activated when reading threat words and viewing masked fearful faces (Whalen et al., 1998).

A recent meta-analysis did not find any significant differences in amygdala volume between children with maltreatment-related PTSD and non-maltreated children (Woon & Hedges, 2008). Later studies have reported increased amygdala volumes in children and adolescents who had been adopted after an experience of early institutionalization (Tottenham et al., 2010). The few studies that have examined the volume of amygdala in adults with a history of childhood maltreatment did not report any significant differences between maltreated and non-maltreated subjects (Andersen et al., 2008). A fMRI study has shown a strong positive correlation between physical abuse and right amygdala response to sad faces in a sample including 20 patients with depression and 16 healthy controls. The heightened amygdala response to sad faces was not a characteristic of individuals with depression, but rather of the subjects with a significant history of maltreatment (Grant et al., 2011).

### 3.2.3 Corpus callosum

The *corpus callosum* (CC) is the thickest band of myelinated fibres in the brain which connects, anatomically and functionally, the right and left hemispheres, allowing them to exchange information. Nerve fibre connections passing through the CC are fully formed before birth, with a rostral-caudal pattern of myelination that continues in young adulthood.

The majority of studies have shown a decrease in *corpus callosum* volume (particularly middle and posterior regions) in maltreated children and adolescents, as well in adults reporting childhood maltreatment. The *corpus callosum* size was more affected by early maltreatment in male than in female subjects (Teicher et al., 2004).

Reduction in the size of *corpus callosum* has been associated with a decrease in communication between the brain hemispheres as demonstrated, in adults with a history of childhood maltreatment, by the dramatic difference in hemispherical activation during the recall of neutral and disturbing memories, evaluated through evoked potentials (Schiffer et al., 1995).

### 3.2.4 Prefrontal cortex

Prefrontal cortex (PFC) consists of several related areas, including orbitofrontal cortex, anterior cingulate (ACC) and anterior prefrontal cortex. Prefrontal functions are related to action planning, decision making, working memory, and attention.

Studies comparing PFC volume of children with maltreatment-related post-traumatic stress disorder and non-maltreated children have yielded inconsistent results (McCrory et al., 2010).

In contrast to the studies on maltreated children, decreased PFC volume in adults with a history of childhood maltreatment has been a consistent finding both in non-clinical sample and in depressed subjects. Adult patients with major depressive disorder, who reported a history of childhood maltreatment, exhibited reduced volume of the rostral anterior cingulate cortex (ACC). This finding supports the hypothesis that the rostral ACC, like the hippocampus, might be vulnerable to prolonged glucocorticoid exposure due to chronic stress, which in turn may decrease its ability to regulate HPA activity in response to future stress, resulting in greater exposure to glucocorticoids (Treadway et al., 2009). Emotional abuse was associated with a reduction in left dorsal medial PFC, even in the absence of physical or sexual abuse in childhood. This volumetric change was independent of gender and it could not be attributed to current psychopathology, supporting the hypothesis that the observed brain differences might be associated with the experience of emotional abuse (van Harmelen et al., 2010).

### 3.3 Interaction between genetic variance and adverse events

Accumulating evidence supports the hypothesis of a gene-environment (GxE) interaction, in which specific polymorphisms exert genetic control of sensitivity to stressful experiences in early life, influencing the causal effect of environmental stressors on depression.

The original work by Caspi et al. (2003) demonstrated that individuals with one or two copies of the short (s) form of the serotonin transporter gene promoter region polymorphism 5-HTTLPR are at higher risk of developing depression in response to stressful life events than people who were homozygous for the long (l) allele. The 5-HTTLPR short allele appears to reduce *in vitro* the transcriptional activity of 5-HTTLPR, resulting in decreased expression of the serotonin transporter (5-HTT).

Emerging preclinical and clinical evidence suggests that the negative sequelae associated with early stress are not inevitable. The presence of positive supports is an important environmental factor in promoting resiliency in maltreated children, even in the presence of a genotype expected to confer vulnerability for psychiatric disorders. Maltreated children with the s/s genotype of 5-HTTLPR and no positive supports had depression scores that were twice as high as the non-maltreated comparison children with the same genotype. Nevertheless, the presence of positive supports reduced the risk associated with maltreatment and with the s/s genotype of 5-HTTLPR, so that maltreated children with this profile had only minimal increases in their depression scores (Kaufman et al., 2004).

GxE studies have been also focused on the role of genes involved in the physiological response to environmental stressors, via HPA axis, in moderating the risk to develop a psychiatric disorder following childhood adverse experiences.



Corticotropin-releasing hormone receptor 1 (CRHR1) is a G protein-coupled receptor localized in frontal cortical areas, forebrain, brainstem, amygdala, cerebellum, and anterior pituitary gland that plays a key role in the regulation of the HPA axis activity in response to stressful events, mediating the action of corticotropin-releasing hormone (CRH) on the pituitary gland to release adrenocorticotrophic hormone (ACTH) that stimulates the production of cortisol in the adrenal cortex. Preclinical studies indicate that persistent hyperactivity of the HPA axis following developmental stress exposure is mediated, at least in part, by a hyperactive CRHR1 system (Lupien et al., 2009). Genetic variants in the corticotropin-releasing hormone receptor (CRHR1) gene polymorphisms appeared to moderate the effect of childhood abuse on the risk for adult depressive symptomatology (Bradley et al., 2008).

Recently, a study has provided preliminary evidence that gene by environment (G  $\times$  E) interactions may play an important role in explaining the differential effectiveness of a given intervention. In 1-to-3-year-old children with externalizing problems, Bakermans-Kranenburg et al. (2008) found a moderating role for the dopamine D4 receptor (DRD4) in a video-feedback intervention designed to improve maternal sensitivity and discipline, showing that the intervention was effective primarily in those children with the DRD4 7-repeat polymorphism.

### 3.4 Epigenetics

The word “epigenetics” refers to processes by which environmental influences can regulate gene activity without altering the underlying DNA sequence. There is growing evidence that epigenetic mechanisms of gene regulation have been implicated in several psychiatric disorders such as depression, drug addiction and schizophrenia (Tsankova et al., 2006).

This epigenetic process is coordinated in large part through the control of chromatin structure. Chromatin is composed of nucleosomes that consist of ~147 base pairs of DNA wrapped around a core of histone proteins. These nucleosomes undergo a supercoiling process, which results in a highly compact structure that permits to control gene expression also by gating access of transcriptional activators to DNA. The structure of chromatin, and hence the access to DNA, is regulated by the direct methylation of DNA and post-translational modifications of histones, both of which can either promote or suppress gene transcription.

Methylation of DNA is a direct chemical modification of a cytosine, by adding a -CH<sub>3</sub> group through a covalent bond. This process is associated with the suppression of gene transcription and, in cases of extensive DNA methylation, with the complete silencing of the associated gene. Modifications of histone proteins include acetylation, phosphorylation, methylation of histones and many other processes, with each modification either positively or negatively regulating the transcriptional activity of the underlying gene.

The regulation of gene expression has been also proposed as a potential mechanism that can mediate both vulnerability and resilience to environmental factors, explaining through which processes early environmental factors may produce long-lasting effects on HPA activity and neuronal function.

“Epigenetic” effects of maltreatment in brain areas, in which structural and functional changes have been observed in adults following maltreatment, have been reported by Roth

et al. (2009), using a rat model of infant maltreatment by a caregiver. This study showed that early maltreatment produced persisting changes in methylation of BDNF DNA, through the lifespan to adulthood, leading to a reduced BDNF gene expression in the adult prefrontal cortex and hippocampus. The changes of BDNF DNA methylation have been demonstrated in the offspring of females that had been previously exposed to maltreatment as pups. This finding suggests the possibility of a trans-generational transmission of changes in gene expression associated with early maltreatment, even in a new generation of animals who had not been exposed to such environmental stressors.

It is well-documented that stress experienced during gestation causes brain and behavioural alterations in offspring that are comparable to those produced by postnatal adversity. Human infants of mothers with high levels of depression and anxiety during the third trimester have increased methylation of the glucocorticoid receptor gene promoter in cord blood cells (Oberlander et al., 2008).

In one of the few epigenetic studies in humans, differences in epigenetic regulation of hippocampal glucocorticoid receptor expression in suicide victims with a history of childhood abuse, as compared with either suicide victims with no childhood abuse or controls, have been observed (McGowan et al., 2009).

Epigenetic modulation of gene transcription has also been implicated in the long-term impact of positive caregiver experiences on adult rat stress responses: adult patterns of DNA methylation of the glucocorticoid receptor gene in the hippocampus, which plays a crucial role in mediating stress responses, are directly associated with the quality of maternal care received in infancy (Weaver et al., 2004). One important finding from this work is that a positive caregiving environment can reverse the epigenetic methylation changes associated with poor maternal care, highlighting the ongoing importance of positive caregiving in influencing the stress response at the biological level.

#### 4. Conclusion

The empirical evidence concerning the association between childhood parental loss, due to death or separation, and adult mood disorders is inconsistent, probably for the important methodological limitations of the studies. On the contrary, past as well as recent findings converge on the conclusion that childhood maltreatment including sexual, physical, and emotional abuse as well as emotional neglect, are associated to the development of adult mood disorders.

Several animal and human studies have shown that childhood adversity produce long-lived hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis which lead to an over-sensitive stress response, that may be the basis of an etiological link to depression in adulthood.

The sustained cortisol response, which may cause brain damage leading to volumetric changes in several critical brain areas, such as hippocampus and prefrontal cortex, produces further disinhibition of HPA axis activity.

There are preliminary evidences of a gene-environment (GxE) interaction in which specific polymorphisms exert genetic control of sensitivity to stressful experiences in early life, influencing the effect of environmental stressors on the development of adult depression.

The epigenetic regulation of gene expression, a process that does not alter the underlying DNA sequence, has been also proposed as a potential mechanism that can mediate the vulnerability to early environmental factors, explaining through which processes they may produce long-lasting effects on HPA activity and neuronal function.

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## **Clinical, Research and Treatment Approaches to Affective Disorders**

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The causes, development and outcomes of disorders are determined by the relationship of psychological, social and cultural factors with biochemistry and physiology. Biochemistry and physiology are not disconnected and different from the rest of our experiences and life events. This system is based on current studies that report that the brain and its cognitive processes show a fantastic synchronization. Written by the foremost experts on Affective Disorders worldwide, this book is characterized by its innovative, refreshing, and highly sensitive perspective on current knowledge of diagnostic, neurobiology, early life stress and treatment of Mood Disorders. The authors share a deep understanding of unique challenges and difficulties involved in Affective Disorders, and have achieved a balance among clinical, research and new treatment approaches to Affective Disorders. The chapters are written in a comprehensive, easily readable, and highly accessible style, stimulating readers, clinicians and researchers.

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Unit 405, Office Block, Hotel Equatorial Shanghai  
No.65, Yan An Road (West), Shanghai, 200040, China  
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元  
Phone: +86-21-62489820  
Fax: +86-21-62489821

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